REMARKS

Reconsideration of the above-identified patent application in view of the amendment above and the remarks below is respectfully requested.

No claims are herein proposed to be canceled or added in this paper. Claims 1, 26, 27 and 30 are herein proposed to be amended in this paper. Therefore, claims 1-9, 11-16, 18-24, 26-27 and 30 are pending and are under active consideration.

Claims 19, 20, 26 and 27[1] stand rejected under 35 U.S.C. 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In support of the rejection, the Patent Office states the following:

> Claims 19 and 20 are indefinite because the limitations of the claims set forth additional steps that are not within claim 1, and thus, the resulting claim fails to fall within the scope of claim 1. Claim 1 is drawn using the transitional phrase "consisting of " which means that the steps recited in the method are practiced to the exclusion of additional steps. However, claims 19 and 20 add an additional step wherein product "is transferred to [] different reaction vessels" and this is confusing in view of the fact that claim 1 excludes methods with additional steps.
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> Claim 26 is indefinite over the rectiation "thereby enabling the immobilization of the amplificate on a surface" because it is not clear if this is meant to be an active process step which requires that the amplificate is immobilized on a surface. The remainder of the body of the claim does not set forth an immobilization step, but the washing of step (e) appears to be reliant on such a step since it does not seem like it would be otherwise possible to wash away part of the nucleic acids but not others. It is particularly important to clarify this aspect of the method since the claims have been amended to recite "consisting of" language in the preamble, and so, if the

[1] Although claims 26 and 27 are not included in the statement of the rejection, claims 26 and 27 are later said to be indefinite, and what appear to be supporting reasons are given. Therefore, Applicant considers the omission of claims 26 and 27 from the statement of the rejection to be a clerical error. Please advise if Applicant is in error.

immobilization is not particularly required, than it is in fact excluded from the scope of the claim. Clarification is required.

> Claim 27 is indefinite over the recitation "thereby enabling the immobilization of the amplificate on a surface" because it is not clear if this is meant to be an active process step which requires that the amplificate is immobilized on a surface. The remainder of the body of the claim does not set forth an immobilization step, but if there is no such step, it is unclear how the chemical function in step (b) is relevant to the claim. Further in step (e) the "labeled or non-labeled nucleic acids" is confusing because it is not clear which label is being referred to since a label is added to some nucleic acid in step (a) and to heteroduplexes in step (e).

Applicant traverses the subject rejection. Insofar as the rejection pertains to claims 19 and 20, the rejection appears to be predicated on the use in claim 1 of the transition term "consisting of," instead of "comprising." However, in view of the fact that Applicant has herein amended claim 1 to recite "comprising," instead of "consisting of" as the transition term, this ground of the rejection has been obviated. Similarly, to the extent that the rejection is predicated on the use of the transition term "consisting of" in claims 26 and 27, this ground has been obviated as Applicant has amended both of these claims to replace "consisting of" with "comprising." In addition, to the extent that the rejection is based on it allegedly not being clear if the recitation in claims 26 and 27 of the language "thereby enabling the immobilization of the amplificate on a surface" is meant to be an active process step, Applicant has amended this language in claim 26 to recite an active process step and has deleted this language from claim 27.

Accordingly, for at least the above reasons, the subject rejection should be withdrawn.

Claims 1-6, 8 and 18-24 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Rice *et al.* (Oncogene (1998) 17, 1807-1812) in view of Gifford (US 5750335)." In support of the rejection, the Patent Office states the following:

Rice *et al.* teach a method for identifying 5-methylcytosine positions in a sample genomic DNA, said method comprising the steps of:

(a) chemically treating a sample genomic DNA obtained from at least one cell in such a way that cytosine and 5-methylcytosine react differently and from products with different base pairing behavior (p. 1811, treatment with sodium bisulfite);

(b) amplifying by means of a polymerase reaction a segment of the genomic DNA obtained in step (a) (p. 1811, second column);

(c) performing steps (a) and (b) on a reference genomic DNA (Figure 3, methylation was determined for eight different cell types, including normal lymphocytes and normal mammary epithelial cells);

Rice *et al.* utilize chemical treatment with sodium bisulfite in a method to identify the location of methylated cytosines in genomic DNA. Treatment with bisulfite results in the conversion of unmethylated cytosine residues to uracil, while methylated cytosine residues remain unchanged. Thus, in a sample where every cytosine was methylated there would be no change in sequence, but in a sample with very low levels of methylation, after PCR there would be thymines where the unmethylated cytosines previously were located. Rice *et al.* effectively introduce mutations nucleic acid sequences via the treatment with sodium bisulfite. When two treated samples are compared, for example a sample that was highly methylated versus one that had low levels of methylation, the treated sequences would have sequence differences at each position where there was differential methylation. Rice et al. utilize a sequencing method to determine the methylation positions after amplification of the sequences, comparing the sequences to the known BRAC1 sequence (p. 1811, 2nd column).

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Rice et al. do not detect the differences between amplified sequences by forming heteroduplexes from the amplified products for the comparison of a test and reference sample.

Gifford teaches a method for identifying sequence differences between two nucleic acids that comprises the steps of:

(d) forming heteroduplexes from two different nucleic acid samples (Col. 3, lines 40-50);

(e) introducing a detectable label into the heteroduplexes of step (d) by means of a reaction which is specific for non-complementary base pairs (Col. 4, lines 15-20), and

(f) determining the position of mismatches in the sample genomic DNA based on the presence and position of the detectable label (Col. 4, lines 5-10, 20-25; also Col. 5, lines 1-12).

Gifford specifically teaches comparing a sample (patient) nucleic acid fragment with a control (normal) nucleic acid fragment (Figure 2).

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It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methylation detection method taught by Rice *et al.* so as to have utilized the mutation detection methods taught by Gifford. One would have been motivated to utilize the methods taught by Gifford in order to achieve the express benefits of the methods taught by Gifford which include achieving "rapid and accurate genetic screening and diagnosis by comparing two nucleic acids for differences in their sequences...to locate previously unknown mutations of a nucleotide sequence, and to identify the sequence itself, where the nature and position of the mutation within a region of the genome is unknown, and where the location of the region itself is unknown (Col. 3, lines 25-40)." The combination would have resulted in a method "consisting of" the steps set forth in instant claim 1. For example, Gifford et al.specifically teach that the identity and position of the mismatch can be determined by determining the nucleotide sequence of the mismatch region. This is not an additional step from those recited in the claim, but simply one means by which step (f) can be accomplished. The sequencing suggested by Gifford et al. is "based on the presence and position" of the label insofar as the portion of nucleic acid to be sequenced in this case would be the portion that was labeled by the method. Likewise, as a different example, Gifford provide that the reference nucleic acids may be immobilized to a solid surface in an array, the test hybridized to the bound reference sequences, and these labeled with the mismatch binding proteins. In this embodiment, the bound hybrids are detected as an indication of the genetic variation between the test sample and the reference nucleic acid. The presence and position of the sequence difference has been determined, at least it is known that the mismatch is within hybrid that has been bound by the binding protein. With regard to claim 6, the result required in claim 6 would have been a necessary property of the practice of the assay taught by Rice *et al.* in view of Gifford. Namely, where there was differential methylation between the sample genomic DNA and any of the reference DNA's

taught by Rice *et al.*, when these were subjected to heteroduplex analysis as taught by Gifford erroneous base pairings would have been produced at the positions at which 5-methylcytosine was located in the sample genomic DNA but not in the reference genomic DNA.

Later in the Office Action, the Patent Office states the following:

> The remarks were previously addressed in the Advisory Action but are addressed again as follows. Regarding applicant's footnote on page 11, the reference to Herman and Hall is an editorial error and has been corrected. The examiner regrets the confusion. Likewise, the inclusion of rejected in the statement of rejection (see response page 12), has been corrected.
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> The claims have been amended to recite methods "consisting of" the recited steps. The methods taught by the combination of Rice et al. in view of Gifford are applied to even these amended claims because the suggested method of the rejections of record would include all of these steps and would not require any steps outside of those recited. Each of the steps recited, for example in claim 1, include a number of different manipulations for the practice of the claimed step, and each is reasonably broad in nature. For example, Applicants argue on page 12 that the amendment of the claims to replace the transition term "comprising" with "consisting of" results in the claims now specifically excluding a sequencing step after fragments containing heteroduplexes are identified. However, this is not entirely accurate. First, claim 1 does not specifically include an "identifying" step as referred to in the argument. Instead, the final step of claim 1 recites "determining the position of 5-methylcytosine in the sample genomic DNA based on the presence and position of the detectable label." This step, as recited, could reasonably include a step wherein the "determining the position" occurs by sequencing the labeled molecules and noting the nucleotide present at the labeled position - thus determining the position "based on the presence and position of the detectable label." Further, as discussed in the rejection in this office action, Rice et al. suggest means for determining the position via use of hybridization to probes in an array, which does not require sequencing. Thus, even the claims which are narrowly drawn using "consisting of" language have sufficient breadth so as to include a potential sequencing step. The method suggested by Rice in view of Gifford (and the additional cited references for later claims) would have made obvious even the narrowly drawn claim as currently pending.

At page 13 of the response, applicant points out that Rice et al. does not teach or suggest any of steps (d)-(f) of claims 1 or 30, and that the rationale used by the office to set forth the obviousness rejection is flawed because "it presupposes that one of ordinary skill in the art at the time of the invention would have been interested in knowing sites of cytosine methylation in a sample segment, without also knowing the entire sequence of the segment." This is not persuasive because (1) Rice et al. are in fact most interested in percent methylation at 30 CpG sites as compared to sites "within the known BRCA1 sequence" (p. 1181), they are not discovering or setting forth a newly discovered sequence and (2) even if Rice et al. were most interested in the sequence and the sequence context, Gifford specifically suggests that their method include a step to "determine the identity and position of the mismatch by determining the nucleotide sequence of the mismatch region (Col. 4, lines 7-9)." As previously noted in this action, the currently drawn claims do not exclude such determination, but only require that the determining of the position is "based on the presence and position of the detectable label." This step taught by Gifford is reasonably a method for carrying out such determination based on the presence and position of the detectable label.

Applicant points out that bisulfite treatment modifies sites of unmethylated cytosines, as is also stated in Rice et al. and in the rejection (page 14 of response, first full paragraph). Applicant further states that such treatment results in dramatic change to the treated sequence, and that insofar as the examiner envisions bisulfite treatment as a mechanism for introducing a mutation the Office is in error "on multiple accounts." However, these multiple accounts are not mentioned, instead, the remarks continue with a second point. It is noted that Gifford specifically teaches that mismatched base pairs can arise via a variety of mechanisms, including "chemical modification of DNA (Col. 2, lines 50-51)." Thus, base differences between two sequences introduced via chemical modification (such as bisulfite treatment) clearly fall within the differences discussed by Gifford et al. In this case, Rice et al. treat a number of different sequences with bisulfite, including samples from "normal" tissues, and then Rice et al. analyze the differential methylation of each relative to the other (see Figure 3). Sequences differences among the different samples in this case would have been the result of chemical modification. Applicant further argues that after treatment with bisulfite, two strands which were formally complementary normally do not anneal due to differences in sequence, and accordingly mismatching cannot occur. This is not persuasive. First, it is an

> attorney argument which is not supported by evidence on the record. Second, Rice et al. teach subsequent amplification of the treated molecules to produce a double strand which could then be compared to a reference sequence which was also bisulfite treated (Rice teaches comparing the bisulfite treated molecules to the "known" BRAC1 sequence). Further still, the method also encompasses the comparison of any of the bisulfite treated molecules of Rice et al. to one another in order to determine differences in methylation among them. Rice et al. treat a number of different sequences with bisulfite, including samples from "normal" tissues, and then Rice et al. analyze the differential methylation of each relative to the other (see Figure 3). Sequences differences among the different samples in this case would have been the result of chemical modification. The bisulfite treated molecules would only have differences at points of differential methylation, and thus would anneal. The rejection is maintained in view of these remarks.
>
> Applicant attempts to construe Gifford as only being applicable to random event mutations, but this reading of Gifford is narrower than Gifford suggests, as previously noted where Gifford discusses different methods that mismatches are the result of chemical treatment of sequences. Finally, applicant's remarks regarding the "ascertainment of the sequence context" have been previously addressed in this advisory action. Therefore, having carefully considered applicant's remarks, the rejection is MAINTAINED. (Emphasis in original.)

Applicant respectfully traverses the subject rejection.

Claim 1, from which claims 2-6, 8 and 18-24 depend, has been amended herein and now recites "[m]ethod for identifying 5-methylcytosine positions in a sample genomic DNA, said method comprising the steps of:

a) chemically treating a sample genomic DNA obtained from at least one cell, cell line, tissue or individual in such a way that cytosine and 5-methylcytosine react differently and form products with different base pairing behavior,

b) amplifying, by means of a polymerase reaction, a segment of the sample genomic DNA obtained in step a),

c) performing steps a) and b) on a reference genomic DNA,

d) forming heteroduplexes from the amplified segments produced in steps b) and c),

e) introducing a detectable label into the heteroduplexes of step d) by means of a reaction, which is specific for non-complementary base pairs, and

f) determining, without sequencing, the position of 5-methylcytosine in the sample genomic DNA based on an identification of the presence and position of the detectable label."

Thus amended, claim 1 now specifically excludes sequencing as part of the determining step. By contrast, Rice et al. specifically teaches that sequencing is an integral part of its method for identifying 5-methylcytosine positions. This is a fundamental difference in approach taken by the claimed method and by Rice et al., and the Patent Office has failed to provide evidence that one of ordinary skill in the art would have been motivated to modify Rice et al. to omit such an integral part of its technique.

Moreover, as apparently acknowledged by the Patent Office, Rice et al. does not teach or suggest forming heteroduplexes between sample and reference amplified segments, introducing a label into the heteroduplexes and determining the position of 5-methylcytosine based on the presence and position of the label. In an attempt to cure this deficiency, the Patent Office relies on Gifford. However, as explained further below, one of ordinary skill in the art would not have been motivated to combine the teachings of Rice et al. and Gifford since Rice et al. is directed at methylation analysis whereas Gifford is directed at mutation analysis. As explained below, because of the differences involved in methylation analysis and mutation analysis, one of ordinary skill in the art would not have been motivated to combine the teachings of disparate references in the manner proposed by the Patent Office.

Bisulfite treated DNA differs chemically and physically in many ways from genomic DNA, especially in length, complexity, base composition and spatial structure:

During the bisulfite treatment, the DNA will be strongly fragmented. The degree of the fragmentation depends on the conditions of the reaction. The longer the reaction lasts, and the higher the temperature is, the greater is the decomposition rate of the DNA. On the other hand, long reaction times are necessary for a complete transformation. Therefore, the bisulfite treated DNA is presented in a complex mixture of fragments having different length and potentially incomplete transformed fragments (see: Grunau et al 2001: Bisulfite genomic sequencing: systematic investigation of critical experimental parameters. Nucleic Acids Res. 2001 Jul 1; 29(13):E65-5). As the incomplete transformed DNA is a source of error for false-positive signals, it must be secured during analysis that only the transformed DNA will be detected.

Bisulfite treated DNA contains other bases than genomic DNA. Through the bisulfite treatment, all unmethylated cytosines are converted into uracil. Uracil is not contained in genomic DNA. Uracil shows the same base pair behavior as thymine. However, there are various amounts of enzymes being able to differ between uracil and thymine.

Bisulfite treated DNA contains a totally different base composition than genomic DNA. Genomic DNA contains four bases. To the contrary, bisulfite treated DNA consists over large stretches of only three bases because all non-methylated

cytosines are converted to uracil. These are at least all cytosines which are located outside the sequence context CpG.

Through the 3-base alphabet, the bisulfite-treated DNA is less complex than the genomic DNA, and sequence repetitions can occur easier. Therefore, the design of specific primers or probes is much more difficult.

A feature of the genomic DNA is the double helix structure. To the contrary, bisulfite-treated DNA is not double-stranded, it is single-stranded. This originates therein, that through bisulfite treatment two DNA strands occur which are not complementary, which do not hybridize with each other. If C is transformed into U on one strand, the complementary G on the reverse strand remains unchanged. A base pairing between the new U and the remaining G is not possible. This is illustrated by the following example:

Before bisulfite treatment:

5'-CCGCTACGAACCCGACATACCCTG-3' upper strand A

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3'-GGCGATGCTTGGGCTGTATGGGAC-5' lower strand B

upper and lower strands are complementary

After bisulfite treatment:

5'-UUGUTAUGAAUUUGAUATAUUUTG-3' upper strand A

| | | | | | | | | | | | | | | | | | | | | | | | | |

3'-GGUGATGUTTGGGUTGTATGGGAC-5' lower strand B

upper and lower strands are no longer complementary

The single-stranded DNA potentially forms possibly short intramolecular double-stranded segments, which are particularly preferred through the small complexity of the bisulfite DNA.

Therefore, genomic DNA and bisulfite-treated DNA differ chemically and physically in various manners. It is not possible to use all kinds of methods for mutation analysis also for methylation analysis. As it is well known in the art, methods can be used theoretically lead many times to bad results.

Because of this, a person of ordinary skill in the art faced with the underlying problem of the invention would not have considered combining Rice and Gifford in the manner proposed by the Patent Office.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

Claims 9, 11-16, 26-27 and 30 stand rejected under 35 U.S.C. 103(a) "as being unpatentable over Rice *et al.* in view of Gifford as applied to claims 1-6, 8 and 18-24 above, and further in view of Koster *et al.* (US 6428955)." In support of the rejection, the Patent Office states the following:

The teachings of Rice *et al.* in view of Gifford are applied herein as applied in the previous rejection. In the method taught by Rice *et al.* in view of Gifford, sodium bisulfite is used which results in the modification of unmethylated cytosines, and therefore mismatches would occur among treated nucleic acids at positions where there was relative differential methylation of sequences. Thus, after bisulfite treatment, one is left with nucleic acids that have mismatches relative to one another if the sequences are differentially methylated. Rice *et al.* in view of Gifford do not teach a method in which the heteroduplex is detected by cleavage of the heteroduplex molecule or in which mass spectrometry is used to analyze the size of the DNA fragments.

Claim 26 differs from claim 1 in that in step (b) the PCR primer is fluorescently labeled and provided with a chemical function thereby enabling the immobilization of the amplificate on the surface, step (e) utilizes a chemical mismatch cleavage methodology, and step (f) utilizes mass spectrometry, whereby in step (g) the presence or presence and position of the 5-methylcytosine within the genomic DNA is deduced from the length of the cleaved nucleic acids. Claim 27 is similar to claim 26 but requires that a detectable label is introduced into the heteroduplex by an enzymatic reaction which is specific for non-complementary base pairs. This limitation is provided in the methods taught by Rice *et al.* in view of Gifford.

Likewise, newly added claim 30 is similar to claim 26, and thus also similar to claim 1. Steps (a)-(d) of claim 30 are similar to those of claim 1. Unlike claim 1, however, claim 30 requires that the heteroduplexes of step (d) are cleaved by a chemical mismatch cleavage reaction. Claim 9 depends from claim 30 and requires that the nucleic acid backbone of the heteroduplex is specifically cleaved at the non-complementarily base paired positions by an enzymatic means. Claims 11-15 also depend from claim 30.

With regard to claims 11-14, Koster *et al.* teach methods for analyzing the size of nucleic acid fragments using mass spectrometry, specifically teaching the use of MALDI-TOF and ESI (Col. 18, line 66-Col. 19, line 11).

With regard to claim 15, which requires that the nucleic acids in step (e) are "adapted" to the performance capacity of the mass spectrometer, Koster *et al.* teach utilizing a variety of PCR amplification methods to obtain PCR products that they analyze using the mass spec (See examples 14-15, for example). With regard to

claim 16, Koster *et al.* teach utilizing nested PCR to amplify products for detection (Examples 5 and 14, for example), a method which uses primers that are set stepwise along the DNA with respect to the inner and outer pairs of primers and produce a series of amplification products, at least one of which is within the mass range detectable by means of mass spectrometry. These PCR primers are considered to be "set stepwise" since they amplify two differently sized products where one is a size "step" down from the other.

Koster *et al.* teaches a method in which a heteroduplex is cleaved by an agent that cleaves the unhybridized portion so that a mismatch results in two products and then detecting these by mass spectrometry to detect the presence of the mismatch (Col. 5, lines 30-40; Col. 23, lines 25-40). Koster *et al.* further teach primers that are labeled with biotin (a means for immobilizing an amplificate on a surface; col. 35, for example) and primers that are labeled with a radioactive label and oligonucleotides that are fluorescently labeled (Col. 49, for example). In addition, as noted previously in this office action, any nucleic acid sequence itself is considered a "chemical function" that would enable the immobilization of the amplificate on a surface. Claims 26 and 27 never actually require the immobilization of the amplificate on a surface, only that such immobilization is "enabled." Nonetheless, Koster further teach methods in which the sequence to be detected is immobilized to a solid support by means of hybridization (Col. 3, lines 60-67).

It would have been prima facie obvious to one of ordinary skill in the art to have modified the method taught by Rice *et al.* in view of Gifford *et al.* so as to have used the amplification and detection methods taught by Koster *et al.* One would have been motivated to use mass spectrometry as a means for detection of nucleic acid fragments in order to take advantage of the express benefits of such a method as taught by Koster *et al.*, who state "the processes of the invention provide for increased accuracy and reliability of nucleic acid detection by mass spectrometry (Col. 5, lines 62-65)." One would have been motivated to use chemical cleavage to detect heteroduplexes by Koster's specific suggestion to do so, and in order to take advantage of an additional method for detecting sequence differences among the potentially differentially methylated sequences taught by Rice et al. Furthermore, it would have been prima facie obvious to have utilized fluorescently labeled primers in place of the radioactively labeled primers taught by Koster *et al.* in order to have provided an alternative labeling method that is safer to use as opposed to using radioactivity in the laboratory.

Applicant respectfully traverses the subject rejection.

Claims 9 and 11-16 depend from claim 30. Claim 30 is patentable over Rice et al. in view of Gifford for at least the same types of reasons discussed in the previous rejection. Kolster fails to cure the deficiencies of Rice et al. and Gifford. Therefore, claims 9, 11-16 and 30 are patentable over the combination of Rice et al., Gifford and Kolster.

Claims 26 and 27 are patentable over the applied combination of references for at least the same types of reasons given above for claim 1.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

Claim 7 stands rejected under 35 U.S.C. 103(a) "as being unpatentable over Rice *et al.* in view of Gifford as applied to claims 1-5, 7-8, 11, 18-25, 28, and 29 above, and further in view of Nazarenko *et al.* (US 6090552)." In support of the rejection, the Patent Office states the following:

> The teachings of Rice et al. in view of Gifford are applied herein as applied in the previous rejection. Rice et al. in view of Gifford do not teach methods wherein the reference DNA is methylated at all CpG positions.
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> However, the inclusion of a methylated control in an assay for the determination of methylation would have been routine at the time the invention was made. Nazarenko et al. teach methods for detecting methylation in samples, and teach the inclusion of methylated control nucleic acids in these assays and in kits for performing these assays (see Col. 37-38 and 49-50, for example). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included in the assays taught by Rice et al. in view of Nazarenko et al. a control which is methylated at all CpG positions in order to have had a standard for comparison of all results against those obtained with a methylated control.

Applicant respectfully traverses the rejection. Claim 7 depends from claim 1. Claim 1 is patentable over Rice et al. in view of Gifford for at least the same types of reasons discussed above.

Nazarenko et al. fails to cure the deficiencies of Rice et al. and Gifford. Therefore, claim 7 is patentable over the combination of Rice et al., Gifford and Nazarenko et al.

Accordingly, for at least the above reasons, the present rejection should be withdrawn.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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Dated: March 22, 2006

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on March 22, 2006

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